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The Prevalence of Antifungal Agents Administration in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective Study

Mona Kargar[1], Alireza Ahmadvand[1], Milad Ahmadvand[1], Molouk Hadjibabaie[1], Kheirollah Gholami[1], Seyed Hamid Khoee[1], Mohammad reza Javadi[1], Ardeshir Ghavamzadeh[2]

[1]Research Center for Rational Use of Drugs, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Hematology-Oncology and SCT Research Centre, Department of Hematology-Oncology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author: Molouk Hadjibabaie
Research Center for Rational Use of Drugs, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
Email: hajibaba@tums.ac.ir

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ABSTRACT

Background: Invasive fungal infections (IFIs) are chief infectious complications in patients undergoing hematopoietic stem cell transplantation (HSCT). However, the diagnosis of fungal infections is difficult, and often empiric treatment initiates. Since there is no data available on the prevalence of antifungal drugs administration in allogeneic HSCT recipients in Iran, we decided to conduct this study.

Methods: This study was a retrospective review of records of patients who received allogeneic HSCT in the Hematology-Oncology, Bone Marrow Transplantation center at Shariati Hospital in Tehran, between August 2009 and August 2010.

Results: Sixty (73.1%) patients consist of 41 men (68.3%) with mean age of 26.3 (± 1.2) years received allogeneic HSCT. Patients received prophylaxis with fulconazole however; in 28 patients (46.7%) it was switched to low dose amphotericin B. Fifteen patients (25%) received treatment with antifungal agents. Amphotericin B was the empiric agent administered. In 3 patients treatment was switched to voriconazole. Neither positive culture nor direct microscopic evidence was available from the obtained specimen. Only in one patient the result of serum galactomannan assay was positive. There were no significant differences in neutropenia duration (P value: 0.54), length of hospital stay (P value: 0.27) and number of patients developed graft versus host disease (P value: 0.07) between patients received antifungal agents with those who did not receive treatment.

Conclusion: In this study HSCT recipients received antifungal agents for prophylaxis. Twenty five percent of patients received treatment with antifungal agents empirically. Improvement in diagnosis of these infections can be helpful and lead to targeted therapy. We suggest larger prospective trials for better assessment of antifungal agent administration.

KEY WORDS: Antifungal agents, Peripheral blood stem cell transplantation, Retrospective Studies, Amphotericin B

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is an effective treatment modality, for a variety of hematologic malignancies.[1] Despite improvement in the prophylaxis and treatment strategies[2] and supportive care measures,[3] infection still is considered as a substantial cause of morbidity and mortality in patients undergoing HSCT,[4, 5] By the advances achieved in the control of bacterial infections after HSCT, invasive fungal infections

(IFIs) are chief infectious complications in these patients.[6] The leading causes of infection in this category are Candida and Aspergillus species.[7] Additionally, infections with less common fungi like Fusarium and Trichosporon species have been reported in this patient population.[8] The incidence of IFI after allogeneic HSCT is estimated to be 10% to 25% in high-risk patients.[9] The mortality rate of these infections may reach to 70% to 90%.[10]

There are many risk factors that have been evaluated for the development of IFI following HSCT. Some of them are neutropenia duration, receiving glucocorticoids, donor type, age,[11] underlying disease,[8, 11] graft-versus-host disease (GVHD),[8,11,12] organ dysfunction (renal, hepatic, or respiratory failure), hyperglycemia, cytomegalovirus or HIV infections,[8] the function of immune system,[8, 9, 13] breakdown of the gut mucosa due to chemotherapy and radiation therapy,[8] use of indwelling devices[9, 13] and iron overload.[8, 9, 13]

Routinely four strategies including prophylactic, empiric, preemptive, and targeted therapy are applied for the management of fungal infections.[14] As a common practice, high risk patients receive prophylaxis against fungal infections.[14] For prophylaxis against Candida infections in patients undergoing HSCT, fluconazole has been administered during the neutropenic period.[15] Whenever possible to identify the infectious fungi, targeted treatment can be implemented.[14] According to EORTC/MSG consensus group, the proved diagnosis of fungal infection in a patient with findings consistent with an endemic mycosis needs at least positive culture obtained from blood or the affected site or evidences from histopathology or direct microscopic observation.[16] However, the diagnosis of fungal infections is difficult due to several factors. One of them is the lack of diagnostic facilities for simple and early detection.[17] Moreover, according to IDSA guideline for neutropenic patients with 5 days of persistent fever after the initiation of broad spectrum antibiotics, in whom no specific cause has been determined; starting empiric antifungal treatment can be considered.[18] Despite the advances achieved in the diagnosis and treatment of fungal infections, unfortunately there are still centers in which the proved diagnosis of fungal infections cannot be made and other strategies have been used for the treatment of suspected and less well documented infections.

Since the introduction of amphotericin B in 1958,[19] the availability of lipid-based formulations of amphotericin B, echinocandins and extended-spectrum triazoles[7] were major advances towards the treatment of fungal infections and provided the clinicians with wider treatment options. Nowadays these agents are prescribed increasingly for the treatment of fungal infections due to increased number of immune compromised and critically ill patients.[20]

In Iran, different studies have addressed the prevalence of IFIs in the setting of solid organ transplantation.[21-23] But to the best of our knowledge, there is no data available on the prevalence of antifungal drugs administration in HSCT setting. So the aim of this study was to assess the prevalence of treatment with antifungal agents in allogeneic HSCT recipients.

MATERIALS AND METHODS

In this study, we present the retrospective review of records of patients who received allogeneic HSCT in the Hematology-Oncology, Bone Marrow Transplantation center at Shariati Hospital in Tehran, Iran, between August 2009 and August 2010. The study protocol was approved by the ethic committee of the institution. Source of stem cells for HSCT in all patients were peripheral blood. Patients with haploidentical or autologous HSCT were excluded from the study. Patients received different conditioning regimens according to the underlying disease and based on the hospital protocols. None of the patients in this center received total body irradiation (TBI) as a part of conditioning regimen.

Definitions

The day of the HSCT procedure was considered to be day 0 and the days after and before that, were named to be + and – respectively. The time between HSCT and hospital discharge was referred to as the recovery period.

Fever was defined as a temperature ≥ 38.3 ^{o}C. Engraftment was considered when ANC counts of ≥

500 $\times 10^3$/L and platelet counts of ≥ 20000$\times 10^3$/L were achieved for three consecutive days without transfusion.

Supportive Cares and Prophylactic Measures

All patients were hospitalized in isolated rooms and received the same care. Patients' nutrition was supported parentally. Phenytoin was administered to patients receiving conditioning regimens containing busulfan for seizure prophylaxis additionally; patients received prophylaxis against nausea and vomiting. Transfusion of blood and platelet were ordered according to patients' condition. GVHD prophylaxis consisted of cyclosporine and low dose methotrexate in patients who received allogeneic HSCT.

Infection Prophylaxis and Treatment

All patients received low dose acyclovir on admission which continued throughout hospitalization for prophylaxis of Herpes Zoster. Also patients received cotrimoxazole for the prevention of Pneumocystis Carinii infection. CMV antigen testing was performed weekly and positive cases were treated accordingly. Additionally, patients received antifungal prophylaxis. Management of fever in neutropenic patients was according to the guideline of Infectious Diseases Society of America (IDSA) on "the use of antimicrobial agents in neutropenic patients with cancer" [18]. For neutropenic febrile patients an appropriate blood cultures were obtained to determine the source of infection before initiation of broad spectrum antibiotics empirically. If the fever episode was persistent after 48 hours and no etiology for the infection was identified, vancomycin was added to the previous medications. Whenever fever continued for more than 5 days after initiating antibiotics and there was no definite source of infection, empiric antifungal treatment was started. Therapy was then modified accordingly.

Statistical Analysis

Cross-checking of extracted data with the original data sheets and patients charts was done rigorously. Tables, absolute frequency, percentage, median, mean, standard error of the mean, maximum and minimum values were used to summarize different types of data as appropriate.

To determine the relationship between distributions of demographic or clinical covariates in allogeneic HSCT patients whether or not receiving treatment with antifungal agents, we used chi-square test or Fisher's exact test for categorical data, independent sample t-test for quantitative data with parametric distributions, and Mann-Whitney U test for quantitative data with non-parametric distribution. All the analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p<0.05$ to reject the null hypothesis.

RESULTS

During the one-year study period, eighty two patients were admitted to the ward. Sixty (73.2%) patients received allogeneic HSCT. Patients consisted of 41 men (68.3%) and 19 women (31.7%) with mean age of 26.3 (± 1.2) years. Thirty two patients (53.3%) received HSCT due to hematologic malignancies; the rest of them received HSCT because of other underlying diseases such as thalassemia, aplastic anemia and a few other infrequent diseases. In fact thalassemia was the most prevalent condition (26.7%) leading to HSCT followed by acute myeloid leukemia (AML) (23.3%) in this set of patients. Median time to engraftment, median duration of neutropenia and median recovery period were 12 (range: 9-32), 8 (range: 2-22) and 21 (range: 12-48) days respectively. Additionally median length of hospitalization was 30 (21-55) days.

Antifungal Administration

All patients (except one) in this study received antifungal prophylaxis with fulconazole 100 mg twice daily orally. One patient was under treatment with posaconazole and amphotericin B before hospitalization. In 28 patients (46.7%) the prophylaxis of fungal infection was switched from oral fluconazole to low dose intravenous amphotericin B (0.3 mg/kg/day) due to the severity of mucositis which made the oral administration of medications impossible for the patients.

Among all of allogeneic HSCT recipient in this study, 15 patients (25%) received treatment with systemic antifungal medications. The prophylactic agent was discontinued upon the initiation of the treatment. Among patients under prophylaxis with amphotericin B, in 4 patients the dose of amphotericin B increased to the therapeutic dose due to the suspected infections. The median duration of antifungal treatment for patients who received the therapeutic doses of amphotericine B was 10 (2-23) days.

Neither positive cultures nor histopathologic or direct microscopic evidences were available from the specimen obtained from patients. However, in one patient the result of serum galactomannan assay was positive.

Empiric treatment with antifungal agent was initiated with amphotericin B in 14 patients however, later in 3 patients; treatment was switched from amphotericin B to voriconazole due to the suspicious of aspergillosis infection.

Characteristics of HSCT recipients and the frequent regimens used for pre transplantation conditioning are summarized in Table 1 and Table 2 respectively.

Table1. Characteristic of Allogeneic HSCT Recipients who Received Treatment with Antifungal Agents and Those who did not Receive Treatment

Characteristics of HSCT recipients	Patients who did not receive treatment with antifungal agents (n=45)	Patients who received treatment with antifungal agents (n=15)	P-values
Male Gender (%)	30 (66.7%)	11 (73.3%)	0.44
Median age year (range)	23 (14-53)	24 (13-47)	0.99
Mean age year ± standard error	26.3 ± 1.4	26.3± 2.4	
Underlying diseases n (%)			
Thalassemia	13 (28.9%)	3 (20.0%)	
AML	11 (24.4%)	3 (20.0%)	
ALL	8 (17.8%)	4 (26.7%)	
AA	5 (11.1%)	-	
CML	3 (6.7%)	-	
MM	2 (4.4%)	1 (6.7%)	
MDS	1 (2.2%)	2 (13.3%)	
Other conditions †	2 (4.4)	2 (13.3%)	
Median engraftment time, day (range)	12.5 (9-20)	12 (10-32)	0.6 ‡
Median fever duration day (range)	6 (1-27)	8 (2-25)	0.09‡
Median infused $CD34^+$ (10^6/kg) (range)	4.9 (1-8.9)	5.2 (2.0-12.1)	0.66‡
Median neutropenia duration day (range)	7 (0-15)	8 (0-22)	0.54‡
Median length of hospitalization day (range)	29 (21-47)	31 (22-55)	0.27‡
Median recovery period day (range)	20 (12-40)	22 (15-48)	0.18‡
Status of underlying disease at HSCT n (%)		0.23	
CR1	15 (33.3%)	4 (26.7%)	
CR2	9 (20.0%)	3 (20.0%)	
CR3	5 (11.1%)	5 (11.1%)	
Not applicable	16 (35.6%)	3 (20.0%)	

AML: Acute Myelogenous Leukemia, ALL: Acute Lymphoblastic Leukemia, AA: Aplastic Anemia, CML: Chronic Myeloid Leukemia, MM: Multiple Myeloma, MDS: Myelodysplastic syndrome, CR: Complete Remission

†Other conditions consisted of one patient with the diagnosis of paroxysmal nocturnal hemoglobinuria and one patient with myelofibrosis in each group

‡ P values are based on Mann-Whitney U test

Table2. Frequent Conditioning Regimens Used for Allogeneic HSCT in Patients who Received Treatment with Antifungal Agents and Those who did not Receive Treatment

Conditioning regimen (underlying diseases)	Patients who did not receive treatment with antifungal agents	Patients who received treatment with antifungal agents
Busulfan/Cyclophosphamide	22	11
Busulfan/Fludarabine/ Antithymocyte globulin	11	-
Busulfan/Cyclophosphamide/Antithymocyte globulin	3	2
Cyclophosphamide /Antithymocyte globulin	5	-

GVHD

Among patients received allogeneic HSCT, acute GVHD appeared in 32 (53.3%) patients and the most frequent involved site was skin (46.9%). Table 3 shows the acute GVHD Severity and the affected organs in patients who underwent treatment with antifungal agents and those who did not receive antifungal treatment.

Table3. Severity of Acute GVHD and the Involved Site in HSCT Recipient

	Patients who did not receive treatment with antifungal agents (n=45)	Patients who received treatment with antifungal agents (n=15)	P value †
Presence of GVHD (%)	21 (46.7%)	11 (73.3%)	0.07
	GVHD severity grade n (%)		0.26
I	12 (57.1%)	3 (27.3%)	
II	5 (23.8%)	5 (45.5%)	
III	4 (19.0%)	3 (27.3%)	
	Organ involved n (%)		0.02
Skin	13 (61.9%)	2 (18.2%)	
Gastrointestinal tract	3 (14.3%)	1 (9.1%)	
Skin and gastrointestinal tract	5 (23.8%)	8 (72.7%)	

† P values are based on Chi-square test

DISCUSSION

Hematology-oncology wards and intensive care units are among the highest consuming antifungal agents in hospitals.[24] It is important to know the data about antifungal agents prescribed in these wards. In this retrospective study we evaluated the prevalence of antifungal medications administered to patients receiving HSCT during early post transplant period in a referral hospital in Tehran.

During this one-year study almost all patients received fluconazole for the prophylaxis of fungal infections; however, in 28 patients the switch to intravenous antifungal prophylaxis was inevitable and they received low dose amphotericin B for this purpose. Although due to the potential toxicity, amphotericin B was more used as a treatment option rather than prophylaxis,[25] the approach of using this drug as a prophylactic agent goes back to the studies conducted in 1990s.[26] In a prospective randomized trial, Koh et al., compared the efficacy of prophylactic use of fluconazole and low-dose amphotericin B against fungal infections in recipients of HSCT. Overall, the study showed that the incidence of proven, suspected or superficial fungal infections was not significantly different between the two groups.[27] Other studies also evaluated using liposomal amphetamine B for prophylaxis.[28-30]

Varieties of antifungal agents are now used for prophylaxis in different centers. For example Martino et al., evaluated 395 recipients of allogeneic HSCT in Spain and reported that 73% of patients received fluconazole, 17% itraconazole and 4% amphotericin B for prophylaxis and 6% did not receive any antifungal agent for this purpose.[11] None of the patients in our study received itraconazole for prophylaxis. Also there are reports of poor tolerability of itraconazole.[31] For example in a cohort of 549 high risk haematology and HSCT recipients Barnes et al., found that itraconazole was poorly tolerated for prophylaxis and therapeutic serum levels were achieved only in 70% of patients.[32]

Fifteen patients (25%) in our study received antifungal medications due to the suspected IFIs. None of the patients received azoles (neither fluconazole nor itraconazole) for the therapeutic purposes. The empiric antifungal drug administered for patients in our study was amphotericin B. However, in a study on sales data of five university hospitals in Germany, de With et al., showed that amphotericin B consumption decreased during the period of 2001-2003 in the hematology-oncology wards which was primarily attributed to increase in voriconazole administration.[24] Additionally, as it is expected the pattern of empirical antifungal

administration is variable in different centers. For example in a retrospective study of four-year antifungal prescription in hematologic patients, Chan et al., reported that echinocandins were accounted for 62% of all antifungal administrations.[33] In contrast none of the patient in our study received this category of antifungal agents. This was probably due to the unavailability of micafungin, and anidulafungin and restricted availability of caspogungin in Iran. Additionally, the cost of the latter drug was not covered by the medication insurance systems at the time of the study. In a meta-analysis, Goldberg et al., compared empirical or preemptive antifungal treatment with placebo, no intervention, or another antifungal treatment in patients with hematologic malignancies. The results showed that azoles were associated with lower mortality compared with amphotericin B. Also administration of liposomal amphotericin B decreased the mortality and IFIs more than other amphotericin B formulations.[34]

Voriconazole is the first line agent for the treatment of aspergillosis infection[35] and during our study it was prescribed when there was a suspicion of aspergillosis infection and due to the considerable high cost it was not used as an option for empiric treatment. This is the same as the study of Chen et al in which they found that voriconazole was infrequently used for empirical therapy and it was prescribed in 23% of all antifungal drug administrations. Additionally, most often it was used for the cases of high clinical suspicion of invasive aspergillosis.[33]

None of the patients in our study were proven cases of IFI and only in one patient the positive results of serum galactomannane test was available. So, the patients received empiric antifungal treatment. Although it is proposed that empiric treatment did not result in considerable decrease in mortality, it led to a significant decrease in the documented or probable IFIs[34] and is considered to be the standard practice in special patient populations.[36] However, this approach may also increase the risk of overtreatment with these agents.[8] One of the patients in our study had a positive serum galactomannane test. In the absence of stronger evidences for proving fungal infections, serum galactomannane test and computed tomography (CT) are helpful measures for the initiation of antifungal treatment and can predict response. For example Ji et al., retrospectively studied 124 patients who received empirical antifungal agents following allogeneic HSCT and concluded that patients with positive serum galactomannane test and/or chest CT scan had significantly higher response rate to empirical antifungal treatment compared with all patients.[36]

We did not observe any significant differences in neutropenia duration (P value: 0.54), length of hospital stay (P value: 0.27) and number of patients developed graft versus host disease (P value: 0.07) between patients received antifungal agents with those who did not receive treatment.

Limitations

The most important restriction in our study was the lack of microbiologic confirmation of the IFIs in this center which is almost the same as most other centers in Iran. This led to the empirical administrations of antifungal drugs. Another limitation is the short time patients' follow up which did not allow us to assess the long-term outcomes. Also it should be noted that the number of patients included in this study was limited. So it is suggested that researchers conduct a prospective larger trial for better assessment of the fungal infections and their treatment.

CONCLUSION

HSCT recipients in this study received antifungal agents for prophylaxis of fungal infections. None of the patients in this study received targeted treatment with antifungal agents and the treatment was implemented empirically. Improvements in diagnosis of these infections can be helpful and lead to targeted therapy.

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